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Description

Topical Preparation and Method for Transdermal Delivery and Localization of Therapeutic Agents

FIELD OF THE INVENTION

[0001] This invention pertains generally to the medical field of topically-applied therapeutic preparations, and particularly to the transdermal delivery and localization of therapeutic agents, for example, to alleviate pain.

BACKGROUND OF THE INVENTION

[0002] Currently there are a number of over-the-counter (OTC) preparations marketed for relief of "minor" muscular aches and pains. None of these agents appears to be effective for moderate-to-severe chronic pain. In fact, it appears that the only topical prescription analgesic specifically marketed for chronic pain is the LIDODERM® Patch which has been available by prescription since the late-1990s.

[0003] Notwithstanding the paucity of topical prescription agents currently available for treatment of moderate-to-severe pain (acute, post traumatic, and chronic), a number of factors make utilization of such preparations attractive and advantageous.

[0004]

In particular, it would be desirable to have available for the relief of

moderate-to-severe pain, an analgesic preparation which may be applied directly to the locus of pain and / or proximate the spinal column for nerves involved in the particular pain under treatment.

[0005] It would further be desirable for this preparation to avoid the systemic effects of analgesic and adjuvant agents, by relieving moderate-to-severe pain while reducing or eliminating systemic analgesics, e.g., non-steroidal anti-inflammatory drugs (NSAIDs) and/or opiates.

[0006] It would further be desirable to provide local anesthetic neural blockade over a sustained and ongoing period without associated appliances (e.g. indwelling catheters) and / or without motor or sympathetic nerve blockade.

[0007] It would further be desirable to relieve moderate-to-severe pain with a reduced dosage frequency.

[0008] Finally, it would be desirable more generally to provide topical preparations and generalized methods which allow therapeutic agents to be delivered by topical application to a patient's skin, such that after penetrating the skin, dispersion of the therapeutic agent is retarded, and prolonged localized effect is thereby achieved.

[0009] Currently, there do not appear to exist products which can achieve these desirable results, and do so with a satisfactory degree of safety and reliability.

SUMMARY OF THE INVENTION

[0010] Disclosed herein is a preparation for topically delivering and localizing therapeutic agents, comprising: a vasoconstrictor for retarding vascular dispersion of a therapeutic agent; and a penetration enhancer for facilitating penetration of the vasoconstrictor and the therapeutic agent through a patient's skin.

[0011] Further disclosed is an associated method of topically delivering and localizing therapeutic agents, comprising the steps of: using a vasoconstrictor for retarding vascular dispersion of a therapeutic agent; in combination with using a penetration enhancer for facilitating penetration of the vasoconstrictor and the therapeutic agent through a patient's skin.

[0012] Also disclosed are various courses of treatment which comprise applying the various disclosed combinations of agents to the patient's skin.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The features of the invention believed to be novel are set forth in the appended claims. The invention, however, together with further objects and advantages thereof, may best be understood by reference to the following description taken in conjunction with the accompanying drawing (s) and appendices summarized below.

[0014] Figure 1 illustrates a preparation in accordance with a first preferred embodiment of the invention, being applied to a pain locus.

[0015] Figure 2 illustrates the preparation of Figure 1, as further prepared and applied for the treatment of pain from acute herpes zoster.

DETAILED DESCRIPTION

[0016] Disclosed herein is method and associated topical preparation by which a variety of therapeutic agents may be delivered by topical application, transmitted into the body through the skin, and then dispersed slowly so that localized therapeutic effects can be maintained for a prolonged period of time and use of these therapeutic agents may be kept at minimum dosages and / or frequency of application.

[0017] As used throughout this disclosure, unless otherwise stated, the specification of concentrations is understood to be by weight, in relation to the *clinically-utilized* preparation. That is, unless otherwise stated, a 5% concentration of a given ingredient would specify that there are to be 5 grams of that ingredient per 100 grams of the *final product as utilized for clinical application to a patient*. Concentrations in pre-mix compositions, not yet diluted to strengths suitable for clinical use, will thus vary upward accordingly, but are still envisioned and encompassed within the scope of this disclosure and its associated claims.

[0018] Figure 1 illustrates a preferred embodiment of the invention, employed as a preparation 1 for alleviating pain. Preparation 1 is topically applied 16 to a patient's skin 17, either at a pain locus, or at a suitable spinal site. This preparation comprises three therapeutic pain agents: a local anesthetic 11; a quick-onset, short-acting non-steroidal anti-inflammatory agent (NSAID) 12; and a long-acting non-steroidal anti-inflammatory agent (NSAID) 13. Preparation 1 further comprises a penetration enhancer 14 for facilitating penetration of local anesthetic 11, quick-onset, short-acting non-steroidal anti-inflammatory agent 12, long-acting non-steroidal anti-

inflammatory agent 13 and vasoconstrictor 15 (discussed below) through a patient's skin 17 to sites of desired action. Finally, preparation 1 comprises a vasoconstrictor 15 for retarding vascular dispersion of local anesthetic 11, quick-onset, short-acting non-steroidal anti-inflammatory agent 12 and long-acting non-steroidal anti-inflammatory agent 13 after these have penetrated the skin surface and entered the vascular system.

[0019] In the preferred embodiment of pain-relief preparation 1, local anesthetic 11 preferably comprises *bupivacaine*. For *bupivacaine*, the onset of action is 2 to 10 minutes, the peak is at 30 to 45 minutes, and the duration of action is 3 to 6 hours. The *bupivacaine* concentration is preferably approximately 5%. However, the *bupivacaine* concentration may acceptably range as low as approximately 2%. The *bupivacaine* concentration may also acceptably range as high as approximately 10%.

[0020] The purpose of local anesthetic 11 is to reduce or block neural transmission of pain. *Bupivacaine* is preferred, because of its distinct physiochemical properties which make it long-acting, well-absorbed through the skin, and which provide it with significant desired differential blocking properties, favoring sensory over motor.

[0021] However, local anesthetic 11 may alternatively comprise a number of other agents as well, alternatively to, or in combination with, *bupivacaine*. These include the following:

[0022] *Carbocaine*, with the generic name *mepivacaine*. This has an intermediate duration of action. Onset is 3-5 minutes, peak is 15-45 minutes, and

duration is 45-90 minutes. This is a shorter duration of action than *bupivacaine*. If used, the concentration ranges from as low as approximately 1% to as high as approximately 10%, preferably approximately 5%. *Mepivacaine* is commercially available for injection in 1%, 1.5%, 2% and 3% solutions.

[0023] *Chirocaine*, with the generic name *levobupivacaine*. If used, the concentration ranges from as low as approximately 0.25% to as high as approximately 10%, preferably approximately 5%. This has a long duration of action. Onset of action is 2-10 minutes, with duration locally 2-4 hours. If used for epidural or peripheral nerve blocks or obstetrical anesthesia, the duration of action is between 3-9 hours.

[0024] *Naropin*, with the generic name *ropivacaine*. This is another long-acting anesthetic. Onset is 1-15 minutes with peak in 20-45 minutes and duration of action 2-6 hours. If used, the concentration ranges from as low as approximately 0.25% to as high as approximately 10%, preferably approximately 5%. This is available commercially as 2.5, 7.5 and 10mg/ml injections.

[0025] *Nesacaine*, with the generic name *chloroprocaine*. This is another short-duration anesthetic. Onset is 6-12 minutes, peak is 10-20 minutes, and duration is 30-60 minutes. If used, the concentration ranges from as low as approximately 0.25% to as high as approximately 15%, preferably approximately 5%. This is available commercially as 1%, 2% and 3% injection.

[0026] *Novocain*, with the generic name *procaine*. This is another short-duration anesthetic. Onset is 5-10 minutes peak is at less than 30 minutes, duration is less than 2 hours. If used, the concentration ranges from as low as approximately 0.25% to as high as approximately 15%, preferably approximately 7%. This is available as 1%, 2% and 10% injections commercially.

[0027] *Xylocaine*, with the generic name *lidocaine*. This is another intermediate-duration anesthetic, available as gel or solution to apply topically usually every 3-4 hours to obtain relief of pain. If used, the concentration ranges from as low as approximately 2% to as high as approximately 15%, preferably approximately 5%. *Lidocaine* is available as a Jelly in 2 and 4% concentrations, and the ointment is available in both 2.5 and 5% concentrations.

[0028] In addition, or alternatively to all of the above, local anesthetic 11 may alternatively comprise *etidocaine*, *ropivacaine*, *benzocaine*, *tetracaine*, *prilocaine* and / or any other similar agent known at present or which may become known in the future. For all of these local anesthetics, if used, the concentration ranges from as low as approximately 0.25% to as high as approximately 20%, with a preferred concentration to be determined from experimental testing.

[0029] In order to provide both quick relief and long-lasting relief, preparation 1 preferably comprises both quick-onset, short-acting non-steroidal anti-inflammatory agent 12; and long-acting non-steroidal anti-inflammatory agent 13. The determining factor in what is quick versus long acting is in

frequency of dose or half life of the drug entity. The shorter the half life, the more frequent the dosing. As used herein, quick-onset, non-steroidal anti-inflammatory agent **12** is any NSAID with *any* oral dosing frequency of more than twice daily. As used herein, a long-acting non-steroidal anti-inflammatory agent **13** is any NSAID with *no* oral dosing frequency of more than twice daily.

[0030] In a preferred embodiment of pain-relief preparation **1**, quick-onset, short-acting non-steroidal anti-inflammatory agent **12** preferably comprises *ketoprofen*. The *ketoprofen* concentration is preferably approximately 10%. However, the *ketoprofen* concentration may acceptably range as low as approximately 5%. The *ketoprofen* concentration may also acceptably range as high as approximately 20%.

[0031] The purpose of quick-onset, short-acting non-steroidal anti-inflammatory agent **12** is to quickly prevent, retard, or reverse the inflammatory and / or algescic response in tissues at a site of injury, irritation or disease and / or at a suitable spinal location. Thus, quick-onset, short-acting non-steroidal anti-inflammatory agent **12** may alternatively comprise: *diclofenac* with a concentration of at least approximately 2% and at most approximately 20%, and with a preferred concentration of approximately 10%; *diflunisal* with a concentration of at least approximately 5% and at most approximately 20%, with a preferred concentration of approximately 10%; *etodolac* with a concentration of at least approximately 2% and at most approximately 20%, with a preferred concentration of approximately 10%; *fenoprofen* with a concentration of at least approximately 10% and at most

approximately 30%, with a preferred concentration of approximately 20%; *flurbiprofen* with a concentration of at least approximately 2% and at most approximately 20%, with a preferred concentration of approximately 10%; *ibuprofen* with a concentration of at least approximately 5% and at most approximately 30%, with a preferred concentration of approximately 20%; *indomethacin* with a concentration of at least approximately 2% and at most approximately 20%, with a preferred concentration of approximately 10%; *tolmetin* with a concentration of at least approximately 2% and at most approximately 20%, with a preferred concentration of approximately 10%, and / or, in suitable concentration, any other similar quick-onset, short-acting non-steroidal anti-inflammatory agent known at present or which may become known in the future.

[0032] As among all of the above quick-onset, short-acting NSAIDs, *ketoprofen* is preferred because it passes most readily through the skin. It is believed that the next best is *Ibuprofen*, then *indomethacin*, and then *diclofenac*.

[0033] In the preferred embodiment of pain-relief preparation 1, long-acting non-steroidal anti-inflammatory agent 13 preferably comprises *piroxicam*. The *piroxicam* concentration is preferably approximately 1%. However, the *piroxicam* concentration may acceptably range as low as approximately 0.5%. The *piroxicam* concentration may also acceptably range as high as approximately 4%.

[0034] The purpose of long-acting non-steroidal anti-inflammatory agent 13 is to prevent, retard or reverse inflammatory and algescic response for a more prolonged and sustained duration at a site of injury, irritation or disease,

and / or via suitable spinal placement. Thus, in alternative preferred embodiments, long-acting non-steroidal anti-inflammatory agent 13 may alternatively comprise: *celecoxib* with a concentration of at least approximately 5% and at most approximately 20%, with a preferred concentration of approximately 10%; *meloxicam* with a concentration of at least approximately 0.5% and at most approximately 2%, with a preferred concentration of approximately 1%; *nabumetone* with a concentration of at least approximately 5% and at most approximately 20%, with a preferred concentration of approximately 10%; *naproxen* with a concentration of at least approximately 2% and at most approximately 20%, with a preferred concentration of approximately 10%; *oxaprozin* with a concentration of at least approximately 5% and at most approximately 20%, with a preferred concentration of approximately 10%; *rofecoxib* with a concentration of at least approximately 0.5% and at most approximately 2%, with a preferred concentration of approximately 1%; *sulindac* with a concentration of at least approximately 2% and at most approximately 10%, with a preferred concentration of approximately 5%; *valdecoxib* with a concentration of at least approximately 0.5% and at most approximately 2%, with a preferred concentration of approximately 1%; and / or, in suitable concentration, any other long-acting non-steroidal anti-inflammatory agent known at present or which may become known in the future.

[0035] As among all of the aforementioned long-acting NSAIDs, *piroxicam* is the most effective long-acting NSAID, has been used for many years with a high degree of safety, and is also among the least expensive.

[0036] Please note all three of local anesthetic 11, quick-onset, short-acting non-steroidal anti-inflammatory agent 12, and long-acting non-steroidal anti-inflammatory agent (NSAID) 13 are provided together in preparation 1, because each has distinct effects, onsets, peaks and durations which – together – provide the most effective action against pain. However, if certain agents were presently available or were to be developed in the future which combine the desirable properties of these three agents 11, 12, 13, and can penetrate the skin as will be further discussed below, this disclosure fully envisions the use of such agents, and the ability to thus eliminate one or more of agents 11, 12, 13. Further, in a treatment situation where the combined effects of agents 11, 12, 13 are not all necessary, this disclosure fully envisions that one or two of these agents may be omitted consistent with the treatment that is warranted. Further, it is recognized that some of the particular agents 11, 12, 13 may be suitable for dispensation only by prescription and / or administration only by a physician and that others may be suitably dispensed over-the counter and applied by an unsupervised patient. Thus, the particular choice of agents 11, 12, 13 may in some circumstances depend upon whether distribution is intended to be with or without prescription and whether administration is intended to be with or without physician supervision. All of the above also applies to antiviral agent 21, see below.

[0037]

In the preferred embodiment of pain-relief preparation 1, penetration enhancer 14 preferably comprises *dimethylsulfoxide (DMSO)* and / or *lecithin*. The purpose of penetration enhancer 14 is to carry the

therapeutic agents (for example, 11, 12 and / or 13 for the pain preparation of Figure 1; also 21 for the viral treatment preparation of Figure 2) and the vasoconstrictor 15 through a patient's skin to sites of desired action.

[0038] Ease of transmission through skin is linearly related to concentration of *DMSO*. Too high a concentration of *DMSO*, however, causes adverse side effects, specifically malodorous breath. Thus, to enhance transmission through the skin of the therapeutic agents (e.g., 11, 12, 13, and / or 21) and the vasoconstrictor 15 as much as possible, but to avoid the adverse side-effects of *DMSO*, the *DMSO* concentration is preferably approximately 10%. The *DMSO* concentration, however, can also be reduced below 10% to further avoid adverse side effects. Finally, if in the future it becomes possible mitigate the side-effects of *DMSO* and thus to employ *DMSO* in concentrations above 10%, this too is a possibility within the scope of this disclosure.

[0039] In an alternative, equally preferred embodiment, penetration enhancer 14 comprises *lecithin*, in a preferred concentration of approximately 10% to 12%, and in an acceptable concentration of at least approximately 2% to 5% and at most approximately 50%. If *lecithin* is employed, then *DMSO* can be eliminated entirely, or its concentration reduced well under 10%, because the *lecithin* itself will enable sufficient transmission of the therapeutic agents (e.g., 11, 12, 13, and / or 21) and the vasoconstrictor 15 through the skin.

[0040] *Lecithin* may optionally be used in combination with *ethoxy diglycol*, or any

similar solvent known or which may become known in the future which that acts to dissolve the active ingredients to allow *Lecithin* to aid in penetration of the skin:

[0041] In alternative preferred embodiments, penetration enhancer 14 may alternatively comprise any other skin penetration enhancers known at present or which may become known in the future, each of can also serve to penetrate the therapeutic agents (e.g., 11, 12, 13, and / or 21) and vasoconstrictor 15 through the skin 17 to the desired sites of action.

[0042] In the preferred embodiment of pain-relief preparation 1, vasoconstrictor 15 preferably comprises *phenylephrine*. The *phenylephrine* concentration is preferably approximately 0.5%. However, the *phenylephrine* concentration may acceptably range as low as approximately 0.25%. The *phenylephrine* concentration may also acceptably range as high as approximately 1.0%.

[0043] The purpose of vasoconstrictor 15 is to retard vascular dispersion of the therapeutic components (e.g., 11, 12, 13, and / or 21) from their site of action, thereby prolonging the duration of the therapeutic effect at anatomical peripheral pain locus and / or the chosen spinal region, and reducing the required dosages and / or dosage frequencies. *Phenylephrine* is preferred, because it is regarded as a very safe agent and has been used safely for many years. However, in alternative preferred embodiments, vasoconstrictor 15 may alternatively comprise: *ephedrine sulfate*, in a concentration of at least approximately 0.1% and at most approximately 1.25%, with a preferred concentration of

approximately 0.5%; *epinephrine*, in a concentration of at least 0.005% and at most 0.02%, with a preferred concentration of approximately 0.01%; *naphazoline*, in a concentration of at least 0.01% and at most 0.2%, with a preferred concentration of approximately 0.1%; *oxymetazoline*, in a concentration of at least 0.01% and at most 0.1%, with a preferred concentration of approximately 0.05%; and / or, in suitable concentration, any other vasoconstrictors known at present or which may become known in the future. Each of these will also serve to prolong the therapeutic effect and reduce necessary dosing by pacing the delivery of the therapeutic agents through vasoconstriction.

[0044] The following inert ingredients, for example, not limitation, may also be added to preparation 1 to provide chemical stability and provide for long shelf life: *polaxmer 407*, *distilled water*, *sorbic acid*, and *potassium sorbate*. These are otherwise not pharmacologically active as therapeutic agents (e.g., to provide pain relief, antiviral effect, etc.), nor are they involved in the transmission of therapeutic agents through the skin, or in causing vasoconstriction.

[0045] Additionally, *isopropyl palmitate* and / or *isopropyl myristate* are lecithin solubilizers, and thus would likely be employed among the inert ingredients, particularly if penetration enhancer 14 comprises lecithin.

[0046] In a further embodiment illustrated in Figure 2, preparation 1 may be used to treat pain from acute herpes zoster. To achieve this, preparation 1 comprises an antiviral agent 21, in addition to – or alternatively to – therapeutic pain-relieving agents 11, 12, and / or 13.

[0047] In this viral-treatment embodiment of preparation 1 illustrated in Figure 2, antiviral agent 21 preferably comprises *2-deoxy-d-glucose*. The *2-deoxy-d-glucose* concentration is preferably approximately 0.2%. However, the *2-deoxy-d-glucose* concentration may acceptably range as low as approximately 0.1%. The *2-deoxy-d-glucose* concentration may also acceptably range as high as approximately 0.4%.

[0048] Antiviral agent 21 may comprise any agent commonly used on viruses manifested by skin eruptions. Thus, in alternative preferred embodiments, antiviral agent 21 may alternatively comprise: *condylox*, with the generic name *podofilox*, topical, at approximately 0.5% concentration, and a concentration range of at least 0.1% and at most 1%; *zovirax*, with the generic name *acyclovir*, cream or ointment, at approximately 5% concentration, and a concentration range of at least 2% and at most 10%; *denavir*, with the generic name *penciclovir*, topical, at approximately 1.0% concentration, and a concentration range of at least 0.5% and at most 4%; *abreva*, with the generic name *docosanol*, topical, at approximately 10% concentration, and a concentration range of at least 5% and at most 15%; and / or, in suitable concentration, any other topically-usable antiviral agents known at present or which may become known in the future, which may be used to treat viruses manifested by skin eruptions.

[0049] As noted earlier, unless otherwise stated, the specification of concentrations throughout this disclosure is understood to be by weight, in relation to the *clinically-utilized* preparation. However, because the combination of a vasoconstrictor and a penetration enhancer is useful as a

base composition for topically delivering and localizing therapeutic agents *independent of the particular therapeutic agents chosen*, it may be desirable to manufacture a vasoconstrictor for retarding vascular dispersion of at least one therapeutic agent in combination with a penetration enhancer for facilitating penetration of the vasoconstrictor and the at least one therapeutic agent through a patient's skin, *without including any therapeutic agent*. This base "pre-mix" composition – which is effectively a topical delivery and localization composition – would then be separately compounded with the particular therapeutic agents to be topically-delivered, and diluted to appropriate clinically-utilized concentrations with suitable inert ingredients such as but not limited to those set forth above. The reason that all percentages set forth in this disclosure are in relation to the *clinically-utilized* preparation is to maintain a consistent and definite baseline for comparing *relative concentrations* of all ingredients. However, it is to be understood that the specification and claiming of a lower concentration percentage for an ingredient of the clinical preparation scales relatively upward and is also intended to encompass a higher concentration percentage in any pre-mix composition.

[0050] Thus, particularly as used in the claims, the term "clinical concentration" refers not only to the particular clinical concentrations specified, but also to "scaled up" concentrations appearing in pre-mix compositions which have not yet fully mixed with all their ingredients and / or diluted down to their ultimate concentrations for clinical use.

[0051] Thus, for example, given a preferred *DMSO* clinical concentration of up to 10% and a preferred *phenylephrine* clinical concentration ranging from .25% to 1.0% as set forth above, it is to be understood that this disclosure and its associated claims would thereby cover any composition comprising *DMSO* and *phenylephrine* in a ratio of approximately 40 to 1 (10% to .25%) or less. Similarly, for example, given a preferred *lecithin* concentration of up to 50% and a preferred *phenylephrine* clinical concentration ranging from .25% to 1.0% as set forth above, it is to be understood that this disclosure and its associated claims would thus cover any composition comprising *lecithin* and *phenylephrine* in a ratio of approximately 200 to 1 (50% to .25%) or less. The same holds true for the relative clinical proportions (ratios) between and among any and all of the many other ingredients also disclosed herein.

[0052]

While upper concentration limits have been stated herein for the various agents 11, 12, 13, 14, 15, 21, it may turn out following clinical trials that higher limits than those stated can be utilized without adverse patient effect. Thus, it is considered possible to utilize upper concentration limits which are in fact 125%, 150%, 175% and even as much as 200% of the upper concentration limits set forth herein, for all of the agents 11, 12, 13, 14, 15, 21 set forth herein. This is to say, for example, that while the stated upper concentration limit for *bupivacaine* is 10%, it may turn out to be possible following clinical trials to employ an upper limit of 12.5%, 15%, 17.5%, and even as high as 20%, and that the same multipliers apply to all of the other agents 11, 12, 13, 14, 15, 21 and their upper concentration

limits set forth herein. The only exception is *lecithin*, which already has an upper limit of 50%, and certainly cannot be 100% since that would foreclose the use of any other agents. Rather, *Lecithin*, as a safe agent, may in fact comprise whatever proportion of preparation 1 is not accounted for by vasoconstrictor 15 and the various therapeutic agents (e.g., 11, 12, 13, 21) employed in any given situation, and in particular, it may well be possible for *lecithin* to thus account for 60%, 70%, 80%, 90%, 95%, and even more, of the overall preparation 1 in clinical form. That is, *lecithin* may account for 100%, minus the percentages of vasoconstrictor 15 and all of the various therapeutic agents, of preparation 1.

[0053] All of preferred ingredients set forth above for the disclosed embodiments of preparation 1 are readily available and are currently utilized in clinical medical therapeutics in various settings. However, the particular combinations disclosed are novel and non-obvious. Additionally, the particular choices of agents disclosed herein, in the disclosed combinations, and / or in the disclosed clinical and relative concentrations, are also novel and non-obvious.

[0054] Preparation 1 in various pain-relief and other embodiments is preferably fabricated and utilized, for example, not limitation, as a topical gel or cream, or with a topical delivery system such as a patch. The topical, e.g., gel or cream is applied 16 directly to the skin 17 at the locus of pain or other ailment to be topically treated, and / or to a suitable spinal location. Sustained effect may be achieved by placing a thin plastic dressing over the applied gel, forming a patch. If applied via a patch, the patch may be

pre-fabricated to comprise preparation 1 therein or thereon as a delivery system, so that patch itself may be applied to the skin at the pain locus and / or at a suitable spinal location to alleviate moderate-to-severe pain, and generally at the treatment locus for whatever treatment is being delivered. The e.g., gel or cream may also, of course, be applied to the patch and the patch then applied to the patient's skin.

[0055] For pain relief, preparation 1 comprising at least one of agents 11, 12, and / or 13 is applied over exquisitely painful areas of the body. Within 20 to 40 minutes, this provides substantial-to-complete pain relief – relief which may be equivalent to that produced by surgical neural blockade. It may also be applied on intact skin including over healed skin scars (for example, following surgery), and over herpes zoster. Application in various body apertures, e.g., ear, nose, mouth, throat, rectum, etc., as well as application to open wounds which have not yet healed over sufficiently to attain skin integrity, is to be avoided. Thus, as used in this disclosure and its associated claims, the term “patient's skin” is intended to refer to intact skin including skin with healed scars, and to non-open skin with herpes zoster.

[0056] Additionally or alternatively, as noted several times above, preparation 1 may be applied – still to a patient's intact skin – along the spinal column where the nerves involved in the particular pain being treated enter the spinal column, thus further relieving areas enervated by those specific nerves. Thus, for example, application of the preparation to the skin overlying various areas of the dorsal spine may relieve pain in the

dermatomes of the nerve roots most proximal to said application.

Placement of preparation 1, e.g., over L 4-5 paravertebral area may relieve lower leg pain ('sciatica'). The same holds true for other areas of the body and other spinal nerves.

[0057] In contrast to the invention disclosed herein, the current treatment of moderate-to-severe pain states is often inadequate, despite the use of potent systemic analgesics, including opiate analgesics. Currently, if patients require potent systemic analgesics, or are unable to achieve effective relief, they are rendered partially-to-fully disabled by their pain, are often unable to work or function effectively in domestic settings, and may become prey to all the consequences of severe chronic pain ("Chronic Pain Syndrome").

[0058] The pain-relief preparation 1 of Figure 1 provides clear promise to effectively control severe pain over prolonged periods of time, with consequent improvement in overall patient function, avoidance or reduction in usage of systemic medications, and consequent reduction in the ill effects of such systemic medications.

[0059] It is important to point out that the scope of this disclosure encompasses preparation 1 using the various ingredients and concentrations disclosed herein, alone or in combination with patches and other delivery systems. This disclosure also encompasses the methods of use of the various agents in the various combinations disclosed herein. This disclosure also encompasses various methods for alleviating pain by applying preparation 1 (and more generally, topically delivering and localizing therapeutic

agents), and prescribing and / or distributing preparation 1 separately or in combination with various delivery systems to alleviate pain (or to provide general therapy).

[0060] While only certain preferred features of the invention have been illustrated and described, many modifications, changes and substitutions will occur to those skilled in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.